REMARKS/ARGUMENTS

A new paper sequence listing and CRF are filed herewith.

Particular paragraphs of the specification have been amended to add sequence identifiers. Also, hyperlinks in the specification have been removed.

Claims 1-83 are pending. Claims 1-38, 48-62 are withdrawn from consideration.

Claim 43 is amended to correct an informality. This addresses the rejection of claim 43 under 35 USC § 112 second paragraph.

Claim 68 is amended to call for a recombinant cell expressing Fortilin. Support for this amendment is found in Example 9, pages 159-160. Accordingly, no new matter is added.

Claims 84-88 are newly added. Support for claims 84-87 is found at pages 150-151, as well as throughout the specification. Support for claim 88 is found at page 109, lines 20-24. Therefore, no new matter is added.

A. Rejections under 35 USC § 112

1. Written Description

The rejection of claims 39-47 and 63-83 under 35 USC § 112 first paragraph as failing to meet the written description requirement is respectively traversed.

The Federal Circuit has stated that the test for the written description requirement is "whether the application relied upon 'reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter.'" *In re Daniels*, 144 F.3d 1452, 1456, 46 USPQ2d 1788, 1790 (Fed. Cir. 1998). See also *Markman v. Westview Instruments, Inc.* 52 F.3d 967, 34 USPQ 2d 1321 (Fed. Cir. 1995) (en banc) ("Claims must be read in view of the specification, of which they are a part."). In rejecting a claim under the written description requirement of 35 U.S.C. §112, first paragraph, the Examiner has the initial burden of presenting

evidence or reasons why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined in the claims. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). Accordingly, the Examiner is required: (1) to set forth the claim limitation not described; and (2) to provide reasons why a person skilled in the art would not have recognized the description of the limitation in view of the disclosure of the application as filed. *Interim Guidelines for the Examination of Patent Applications Under 35 USC 112, Paragraph 1*, Chisum on Patents, vol. 3, §7.04[1][c].

The Guidelines state that the "written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus."

Claims 39-47 and 63-83 are directed to Fortilin polypeptides, including Fortilin variants. In rejecting the claims, the Office Action contends that no biologically active Fortilin variants have been disclosed, and that no structure-function relationships have been described. However, sufficient identifying characteristics of Fortilin have been disclosed to show that Applicants were in possession of the claimed Fortilin polypeptides.

The specification describes the human Fortilin amino acid sequence and compares the human sequence to those of other species. Figure 1A of the specification shows the human Fortilin sequence aligned with rabbit, mouse, chicken, insect (*D. melanogaster*), nematode (*C. elegans*), yeast (*S. cerevisiae*) and rice Fortilin sequences. As described on page 18, this

alignment indicates that Fortilin is a highly conserved protein, with human and mouse sequences displaying 95% sequence identity. Even between human and insect, about half of the residues (85 out of 172 total amino acids in the human Fortilin sequence) are identical.

As is well known, conserved residues of a protein are considered to be important for protein function. The idea is that amino acid substitutions occurring at important residues are disfavored during evolution since changes to important residues would disrupt protein activity. Therefore, the conserved residues that make up half of the amino acid sequence of Fortilin are expected to be important for function.

On top of this, many of the amino acid positions that vary among Fortilin sequences involve conservative amino acid substitutions. For example, residue 3 is the hydrophobic residue isoleucine (I) in human and the hydrophobic residue valine (V) in rice; residue 21 is the basic amino acid arginine (R) in humans and the basic amino acid lysine (K) in insect and other invertebrates, and residue 153 is the acidic amino acid glutamic acid (E) in humans and the acidic amino acid aspartic acid (D) in nematode and rice. The conserved chemical nature of these residues indicates that these amino acid positions are also important for function.

Thus, the sequence alignment identifies certain amino acid positions as invariant and important, other positions as variable but functionally conserved, and the rest as variable to a much greater extent. Based on this information, a person of skill in the art would recognize that Fortilin variants retaining biological activity could be prepared by changing Fortilin amino acids at variant residues while keeping the conserved residues intact. This can be accomplished, for example, by replacing a variant residue with a chemically similar residue, or by replacing a variant residue of one Fortilin sequence (i.e., human) with the corresponding amino acid residue found in the Fortilin sequence of a different species (i.e., mouse).

Moreover, the specification also provides methods to assay for Fortilin activity. For example, Fortilin can be assayed by determining its specific binding to p53 (Example 2) or MCL1 (Example 6), or by determining its effects on p53-mediated apoptosis (Example 3). Thus, the specification describes ways in which the activity of Fortilin variants can be determined.

In sum, the specification describes and identifies the position of physically conserved residues, functionally conserved residues, and variable residues of the Fortilin sequence. Those of skill in the art would recognize that biologically active Fortilin variants are those that have amino acid changes at the variable positions of the protein. This, plus the ability to determine the activity of Fortilin variants by assays described in the specification, provides sufficient guidance to identify and generate biologically active Fortilin variants.

The specification teaches the structure of biologically active Fortilin variants and correlates structure with function for conserved residues of the protein. In doing so, these teachings provide more than enough identifying characteristics of Fortilin variants to show that Applicants were in possession of the claimed Fortilin polypeptides. As such, claims 39-47 and 63-83 satisfy the written description requirement.

2. Enablement

The rejection of claims 39-47 and 63-83 under 35 USC § 112 first paragraph as failing the enablement requirement is respectively traversed. The Office Action contends that there is insufficient description of Fortilin variants. However, as noted above, the specification discloses Fortilin variants, teaches those skilled in the art how to prepare such variants, and teaches how to measure Fortilin activity of such variants. Taken together, these teachings provide enough information to enable those in the art to make and use Fortilin variants.

Moreover, the specification teaches that over half of the amino acid positions in the Fortilin polypeptide sequence are either conserved or involve known, conservative substitutions. This means that any experimentation required by the claims is limited to variable amino acid positions, which are expected to be changed without adversely affecting Fortilin activity. Although altering these variable positions may involve some experimentation, a considerable amount of experimentation is permissible if it is merely routine. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); MPEP § 2164.06. In the present case, methods for changing or deleting amino acids are well known and routine in the art. Thus, the claims do not involve an undue amount of experimentation.

The amount of information provided in the specification is more than sufficient to allow those skilled in the art to practice the claimed invention without undue experimentation. Accordingly, claims 39-47 and 63-83 satisfy the enablement requirement.

B. <u>Rejections under 35 USC § 102</u>

The rejection of claims 39, 40, 44, 63, 66 and 67 as anticipated variously by Teshima et al. (J. Immunol., 1998) or by Sturzenbaum et al. (BAA, 1998) is respectfully traversed. Teshima et al. teach that macrophages treated with Macrophage Colony-Stimulating Factor (M-CSF) release Fortilin protein. Sturzenbaum et al. teach that earthworms exposed to the heavy metal Cd have higher levels of Fortilin. However, neither reference teaches a substance that contacts the Fortilin polypeptide.

"To anticipate a claim, the reference must teach every element of the claim." MPEP § 2131. In the present case, the references fail to achieve this standard.

Claims 39, 40, 44, 63, 66 and 67 call for a modulator "contacting the Fortilin polypeptide." In the Teshima *et al.* reference, the cytokine M-CSF is added to macrophages.

There is no evidence that M-CSF contacts the Fortilin polypeptide. As is known, M-CSF acts by binding to a receptor present on the surface of a cell. *See e.g.,* Fixe and Praloran (Exhibit A) at page 33, 1st col., 2nd paragraph. Receptor binding triggers an intracellular cascade that mediates M-CSF action. In other words, M-CSF acts on macrophages extracellularly and does not enter the cells.

Accordingly, there is no evidence that Teshima et al. teaches or suggests a modulator "contacting the Fortilin polypeptide." Because all claim elements are not taught, claims 39, 40, 44, 63 and 67 are not anticipated by Teshima *et al.*

The Sturzenbaum et al. reference describes experiments where Cd added to whole earthworms leads to changes in Fortilin expression . As the authors admit, it is not clear how Cd exerts its effects (page 303, lines 9-13). For example, the increase in Fortilin mRNA expression could be an indirect result of stress or inflammation, or could be a result of additional biotic or abiotic factors. Moreover, there is no evidence that Sturzenbaum teaches or suggests that Cd acts by contacting Fortilin polypeptides, which is an element of the claimed invention. Because all claim elements are not taught, claims 39, 40, 44, 63, 66 and 67 are not anticipated by Sturzenbaum et al.

The rejection of claims 68, 69, 75-77, 79 and 83 as anticipated variously by Teshima *et al.* or by Sturzenbaum *et al.* is respectfully traversed. As amended, claims 68, 69, 75-77, 79 and 83 call for contacting a candidate modulator with a recombinant cell expressing the Fortilin polypeptide.

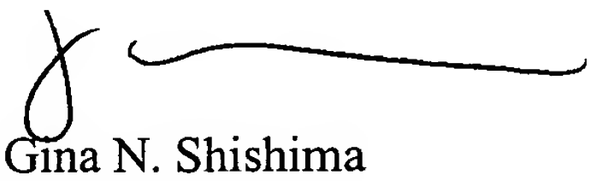
Teshima *et al.* describe the addition of M-CSF to cultured resident peritoneal macrophages, not recombinant cells. Similarly, Sturzenbaum et al. describe the addition of Cd to

whole earthworms, not recombinant cells. Because neither reference teaches or suggests contacting a modulator with a recombinant cell, 68, 69, 75-77, 79 and 83 are not anticipated.

In view of the foregoing amendments and remarks, Applicants submit that the present application is in condition for allowance. A Notice of Allowance is therefore respectfully requested.

The Examiner is invited to contact the undersigned attorney at (512) 536-3081 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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